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EXAMINER	
TRAN, MY CHAU T	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 03/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,240	SHAIR ET AL.	
	Examiner	Art Unit	
	MY-CHAU T TRAN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-33 and 48-68* is/are pending in the application.

4a) Of the above claim(s) *8,11-17,21-25,27-29,50-52,56 and 58-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-7,9,10,18-20,26,30-33,48,49,53-55,57 and 68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Applicant's amendment filed 12/14/2004 is acknowledged and entered. Claims 1, and 34-47 have been canceled. Claims 3, 7, 9, and 32 have been amended. Claims 48-68 have been added.

2. Claims 2-33, and 48-68 are pending.

Election/Restrictions

3. Claims 1, and 34-47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to ***nonelected inventions***, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 06/24/2003. However, applicant has canceled claims 1, and 34-47 by the amendment filed 12/14/2004.

4. Applicant has elected the following species for the elected invention (Claims 2-33, and newly added claims 48-68) in the reply filed on 6/24/2003 and 6/7/2004:

a. A species of test compound. Applicant elected small molecule, which is Taxol.

b. A species of molecular sensor. Applicant elected 2,3-diaminonaphthalene (DAN), which is attached to the solid support via an amide bond shown in figure 4.

c. A species of decoding tag. Applicant elected inert halogenated compound.

d. A species of inducible reporter gene. Applicant elected nitric oxide synthase.

e. A species of reporter gene product. Applicant elected nitric oxide.

f. A species of chemical compound. Applicant elected nitric oxide.

g. A species of cell. Applicant elected yeast.

h. A species of solid support. Applicant elected solid phase resin beads (e.g., aminomethyl-TENTAGEL resin).

5. Claims 8, 11-17, 21-25, and 27-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to ***nonelected species***, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6/24/2003 and 6/7/2004.

6. The newly added claims 50-52, 56, and 58-67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to ***nonelected species***, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6/24/2003 and 6/7/2004.

7. Thus, claims 2-7, 9, 10, 18-20, 26, 30-33, 48, 49, 53-55, 57, and 68 are treated on the merit in this Office Action.

Priority

8. This application claims benefit to a provisional application under 35 U.S.C 119(e). The provisional application 60/273,736 filed 3/5/2001.

Withdrawn Objection(s) and /or Rejection(s)

9. The objection to the disclosure because it contains an embedded hyperlink and/or other form of browser-executable code has been withdrawn in light of applicant's amendments of the specification filed on 12/14/2004.

10. The rejection of claims 2-3, and 32 under 35 USC 112, first paragraph (written description) has been withdrawn in light of applicant's amendments of claims 3, and 32.

11. The rejection of claims 2-3, and 33 under 35 USC 112, first paragraph (written description) has been withdrawn in light of applicant's amendments of claim 3.

12. The rejections of claims 2-7, 9-10, 18-20, 26, and 30-33 under 35 USC 112, second paragraph, as being indefinite have been withdrawn in light of applicant's amendments of claims 3, 9, and 32.

13. The rejection of claims 2, 10, 18-20, 26, and 30-31 under 35 USC 102(b) as being anticipated by Burbaum et al. (US Patent 5,876,946) has been withdrawn in light of applicant's addition of claim 54. ***However***, this rejection was rewritten in order to address the newly added claim 54.

14. The rejection of claims 2-4, 10, 18, and 26 under 35 USC 102(b) as being anticipated by Borchardt et al. (*Chemistry & Biology*, **1997**, 4(12), pgs. 961-968) has been withdrawn in light of

applicant's addition of claim 54. ***However***, this rejection was rewritten in order to address the newly added claim 54.

15. The rejection of claims 2-4, 10, 18, and 33 under 35 USC 102(b) as being anticipated by Still et al. (US Patent 5,565,324) has been withdrawn in light of applicant's addition of claim 54. ***However***, this rejection was rewritten in order to address the newly added claim 54.

16. The rejection of claims 2-4, 10, 18, 26, and 33 under 35 USC 103(a) as being obvious over Still et al. (US Patent 5,565,324) and Ashby et al. (US Patent 5,569,588) has been withdrawn in light of applicant's addition of claims 53, 54, and 68. ***However***, this rejection was rewritten in order to address the newly added claims 53, 54, and 68.

17. The rejection of claims 2-7, 9-10, 18-20, 30-31, and 33 under 35 USC 103(a) as being obvious over Still et al. (US Patent 5,565,324) and Misko et al. (*Analytical Biochemistry*, **1993**, 214(1), pgs. 11-16) has been withdrawn in light of applicant's addition of claims 53, 54, 57, and 68. ***However***, this rejection was rewritten in order to address the newly added claims 53, 54, 57, and 68.

18. Claims 2-7, 9, 10, 18-20, 26, 30-33, 48, 49, 53-55, 57, and 68 are treated on the merit in this Office Action.

Maintained Rejection(s)

Claim Rejections - 35 USC § 112

19. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

20. Claims 2-7, 9-10, 18-20, 26, and 30-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The instant claim 2 recites a method of identifying a test compound that affects a biological event of interest. The method comprises the steps of: 1) providing a plurality of test compounds; 2) providing cells containing an inducible reporter gene, wherein expression of the reporter gene results in the production of a reporter gene product; 3) contacting the cells with the plurality of test compounds; and 4) identifying test compounds which promote or inhibit a biological event based on production of the reporter gene product. The reporter gene product is secreted by the cell, detectable, and its the presence indicates occurrence or non-occurrence of a selected biological event.

The specification disclosure does not sufficiently teach the claimed method of identifying a test compound that affects a biological event of interest wherein the biological event of interest is being detected using ***any*** type of inducible reporter gene that produced a product, which is secreted by the cell and is detectable. The claimed method encompasses a broad genus of

reporter genes that is use to detect biological event of interest, e.g. β-lactamase, luciferase, secreted alkaline phosphatase or green fluorescent protein. The specification description is directed to a screening method for detecting compound that affect protein binding event using nitric oxide synthase wherein the nitric oxide, i.e. reporter gene product, is secreted by the cell and is detected by nitric oxide sensor (see specification e.g. pg. 16, line 19 to pg. 17, line 4; pg. 18, line 8 to pg. 20, line 2; pg. 21, line 11 to pg. 23, line 15; fig. 2-6). The specification examples 2-8 are drawn to screening methods for detecting compound that affect protein binding event using nitric oxide synthase wherein the nitric oxide, i.e. reporter gene product, secreted by the cell is detected by nitric oxide sensor (see specification pages 27-36). This method clearly does not provide an adequate representation regarding a screening method that identifying test compound that affects a biological event of interest using ***any*** type of inducible reporter gene that produced a product, which is secreted by the cell and is detectable. Thus the specification does not teach the claimed method of identifying a test compound that affects a biological event of interest wherein the biological event of interest is being detected using ***any*** type of inducible reporter gene that produced a product, which is secreted by the cell and is detectable.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

With the exception of screening method for detecting compound(s) that affect the protein binding event using nitric oxide synthase wherein the nitric oxide, i.e. reporter gene product, secreted by the cell is detected by nitric oxide sensor disclosed by the specification, the skilled artisan cannot envision the method of identifying a test compound that affects a biological event of interest wherein the biological event of interest is being detected using ***any*** type of inducible reporter gene that produced a product, which is secreted by the cell and is detectable. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

In the present instance, the specification does not teach claimed method identifying a test compound that affects a biological event of interest wherein the biological event of interest is being detected using ***any*** type of inducible reporter gene that produced a product, which is

secreted by the cell and is detectable. Therefore, only the screening method for detecting protein binding event using nitric oxide synthase wherein the nitric oxide, i.e. reporter gene product, secreted by the cell is detected by nitric oxide sensor, but not the full breadth of the claim method meet the written description provision of 35 U.S.C 112, first paragraph.

21. Claims 2-3, and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The instant claim 2 recites a method of identifying a test compound that affects a biological event of interest. The method comprises the steps of: 1) providing a plurality of test compounds; 2) providing cells containing an inducible reporter gene, wherein expression of the reporter gene results in the production of a reporter gene product; 3) contacting the cells with the plurality of test compounds; and 4) identifying test compounds which promote or inhibit a biological event based on production of the reporter gene product. The reporter gene product is secreted by the cell, detectable, and its the presence indicates occurrence or non-occurrence of a selected biological event. Claim 3 claimed that the plurality of test compounds is attached to a solid support through a cleavable linkage. Claim 5 claimed that the solid support is associated with a molecular sensor.

The specification disclosure does not sufficiently teach the claimed method of identifying a test compound that affects a biological event of interest wherein ***any*** type of molecular sensor

is use to detect the reporter gene product wherein the production of the reporter gene product identifying the test compound(s) that affect a biological event. The claimed method encompasses a broad genus of molecular sensor that is use to detect the reporter gene product in order to identify test compound(s) that affect a biological event, e.g. fluorescent label, dendrimer, or green fluorescent protein. The specification description is directed to the use of nitric oxide sensor to detect nitric oxide produce by nitric oxide synthase in the screening method for detecting compound(s) that affected protein binding event (see specification e.g. pg. 16, line 19 to pg. 17, line 4; pg. 18, line 8 to pg. 20, line 2; pg. 21, line 11 to pg. 23, line 15; fig. 2-6). The specification examples 2-8 are drawn to the use of nitric oxide sensor to detect nitric oxide produce by nitric oxide synthase in the screening method for detecting compound(s) that affected protein binding event (see specification pages 27-36). This method clearly does not provide an adequate representation regarding the claimed method of identifying a test compound that affects a biological event of interest wherein ***any*** type of molecular sensor is use to detect the reporter gene product wherein the production of the reporter gene product identifying the test compound(s) that affect a biological event. Thus the specification does not teach the claimed method of identifying a test compound that affects a biological event of interest wherein ***any*** type of molecular sensor is use to detect the reporter gene product wherein the production of the reporter gene product identifying the test compound(s) that affect a biological event.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons

of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

With the exception of the use of nitric oxide sensor to detect nitric oxide produce by nitric oxide synthase in the screening method for detecting compound(s) that affected protein binding event disclosed by the specification, the skilled artisan cannot envision the method of identifying a test compound that affects a biological event of interest wherein ***any*** type of molecular sensor is use to detect the reporter gene product wherein the production of the reporter gene product identifying the test compound(s) that affect a biological event. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

Additionally, Cf. University of Rochester v G.D. Searle & Co., Inc., Monsanto Company, Pharmacia Corporation, and Pfizer Inc., No. 03-1304, 2004 WL 260813 (Fed. Cir., Feb. 13, 2004) held that:

Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods.

In the present instance, the specification does not teach claimed method identifying a test compound that affects a biological event of interest wherein ***any*** type of molecular sensor is use to detect the reporter gene product wherein the production of the reporter gene product identifying the test compound(s) that affect a biological event. Therefore, only the method of using a nitric oxide sensor to detect nitric oxide produce by nitric oxide synthase in the screening method for detecting compound(s) that affected protein binding event, but not the full breadth of the claim method meet the written description provision of 35 U.S.C 112, first paragraph.

New Rejection(s) – Necessitated by Amendment

Claim Rejections - 35 USC § 112

22. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

23. Claim 55 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The instant invention recites the method of identifying a test compound that affects a biological event of interest. The method comprises the steps of 1) providing a plurality of test compounds; 2) providing cells containing an inducible reporter gene; 3) releasing the test compounds from the solid supports; 4) contacting the cells with the plurality of released test compounds; and 5) identifying test compounds which promote or inhibit the selected biological event based on detection of the reporter gene product by the detecting agent.

The specification disclosure does not sufficiently teach the claimed method of identifying a test compound that affects a biological event of interest wherein the biological event of interest is being detected using ***any*** type of inducible reporter gene that produced a product, which is secreted by the cell and is detectable. The claimed method encompasses a broad genus of reporter genes that is use to detect biological event of interest, e.g. β-lactamase, luciferase, secreted alkaline phosphatase or green fluorescent protein. The specification description is directed to a screening method for detecting compound that affect protein binding event using nitric oxide synthase wherein the nitric oxide, i.e. reporter gene product, is secreted by the cell and is detected by nitric oxide sensor (see specification e.g. pg. 16, line 19 to pg. 17, line 4; pg. 18, line 8 to pg. 20, line 2; pg. 21, line 11 to pg. 23, line 15; fig. 2-6). The specification examples 2-8 are drawn to screening methods for detecting compound that affect protein binding event using nitric oxide synthase wherein the nitric oxide, i.e. reporter gene product, secreted by the cell is detected by nitric oxide sensor (see specification pages 27-36). This method clearly does not provide an adequate representation regarding a screening method that identifying test

compound that affects a biological event of interest using ***any*** type of inducible reporter gene that produced a product, which is secreted by the cell and is detectable. Thus the specification does not teach the claimed method of identifying a test compound that affects a biological event of interest wherein the biological event of interest is being detected using ***any*** type of inducible reporter gene that produced a product, which is secreted by the cell and is detectable.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

With the exception of screening method for detecting compound(s) that affect the protein binding event using nitric oxide synthase wherein the nitric oxide, i.e. reporter gene product, secreted by the cell is detected by nitric oxide sensor disclosed by the specification, the skilled artisan cannot envision the method of identifying a test compound that affects a biological event of interest wherein the biological event of interest is being detected using ***any*** type of inducible reporter gene that produced a product, which is secreted by the cell and is detectable. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable

due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

In the present instance, the specification does not teach claimed method identifying a test compound that affects a biological event of interest wherein the biological event of interest is being detected using ***any*** type of inducible reporter gene that produced a product, which is secreted by the cell and is detectable. Therefore, only the screening method for detecting protein binding event using nitric oxide synthase wherein the nitric oxide, i.e. reporter gene product, secreted by the cell is detected by nitric oxide sensor, but not the full breadth of the claim method meet the written description provision of 35 U.S.C 112, first paragraph.

24. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

25. Claim 68 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 68 recites the limitation "the linkage" in line 1. There is insufficient antecedent basis for this limitation in the claim 2. There is no recitation of a 'linkage' in claim 2, and thus the limitation "the linkage" of claim 68 lack antecedent.

Claim Rejections - 35 USC § 102

26. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

27. Claims 2, 10, 18-20, 26, 30-31, and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Foulkes et al. (US Patent 5,580,722). *It is noted that this rejection is rewritten to address the newly added claim 54.*

The instant invention recites a method of identifying a test compound that affects a biological event of interest. The method comprises the steps of: 1) providing a plurality of test compounds; 2) providing cells containing an inducible reporter gene, wherein expression of the reporter gene results in the production of a reporter gene product; 3) contacting the cells with the plurality of test compounds; and 4) identifying test compounds which promote or inhibit a biological event based on production of the reporter gene product. The reporter gene product is a) secreted by the cell; b) detectable; and c) its presence indicates occurrence or non-occurrence of a selected biological event.

Foulkes et al. teach the method of determining whether a chemical not previously known to be a modulator of protein biosynthesis is capable of specifically transcriptionally modulating the expression of a gene encoding a protein of interest (refers to instant claims 2, 10, 18, and 54) (see e.g. Abstract; col. 11, lines 12-29; col. 11, line 60 to col. 12, line 20; col. 18, line 43 to col. 19, line 3; col. 93, Claim 1). The method comprises the step of: (a) contacting a sample which contains a predefined number of identical eukaryotic cells (refers to the instant claimed step of

providing cells and claim 26) with a predetermined concentration of the chemical to be tested (refers to the instant claimed step of providing a plurality of test compounds and claim 10), each such cell comprising a single DNA construct consisting essentially of in 5' to 3' order (i) a modulatable transcriptional regulatory sequence of the gene encoding the protein of interest, (ii) a promoter of the gene encoding the protein of interest, and (iii) a reporter gene which expresses a polypeptide (refers to instant claimed reporter gene product) capable of producing a detectable signal, coupled to, and under the control of, the promoter, under conditions such that the chemical if capable of acting as a transcriptional modulator of the gene encoding the protein of interest, causes a measurable detectable signal to be produced by the polypeptide expressed by the reporter gene (refers to the instant claimed contacting step and claim 18); (b) quantitatively determining the amount of the signal so produced; and (c) comparing the amount so determined with the amount of produced signal detected in the absence of any chemical being tested and upon contacting the sample with other chemicals so as to thereby identify the chemical as a chemical which causes a change in the detectable signal produced by the polypeptide, and determining whether the chemical specifically transcriptionally modulates expression of the gene associated with the treatment of one or more symptoms of the cardiovascular disease (step (c) refers to the instant claimed identifying step) (see e.g. col. 11, lines 12-29; col. 11, line 60 to col. 12, line 20; col. 18, line 43 to col. 19, line 3; col. 93, Claim 1). The protein of interest includes nitric oxide synthase (refers to instant claims 19-20, and 30-31) (see e.g. col. 22, lines 1-21). Thus the method of Foulkes et al. anticipates the presently claimed method.

28. Claims 2-4, 10, 18, 26, and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Borchardt et al. (*Chemistry & Biology*, **1997**, 4(12), pgs. 961-968). *It is noted that this rejection is rewritten to address the newly added claim 54.*

The instant invention recites a method of identifying a test compound that affects a biological event of interest. The method comprises the steps of: 1) providing a plurality of test compounds; 2) providing cells containing an inducible reporter gene, wherein expression of the reporter gene results in the production of a reporter gene product; 3) contacting the cells with the plurality of test compounds; and 4) identifying test compounds which promote or inhibit a biological event based on production of the reporter gene product. The reporter gene product is a) secreted by the cell; b) detectable; and c) its presence indicates occurrence or non-occurrence of a selected biological event.

Borchardt et al. teach methods of detecting small molecule-protein interaction within yeast cells (refers to instant claims 2, 18, and 54) (see e.g. Abstract; pg. 962, right col., lines 1-12; pg. 963, right col., line 41 to pg. 964, right col. 25; pg. 965, left col., line 15 to pg. 966, right col., line 8). The methods comprise the steps of contacting the small molecules with the yeasts cell (refers to instant claim 26), and detecting the small molecule-protein binding via of cell growth or lack of cell growth (see e.g. pg. 963, right col., line 41 to pg. 964, right col. 25; pg. 965, left col., line 15 to pg. 966, right col., line 8). In the growth inhibition assay the binding of rapamycin to its protein targets (refers to instant claimed reporter gene) results in yeast cell arrest (refers to instant claimed reporter gene product) and as a result inhibition of growth (see e.g. pg. 963, right col., line 41 to pg. 964, right col. 25; fig. 3). The small molecules are attached to resin via a photocleavable linker wherein the small molecules are release by irradiation with ultraviolet light (refers to instant claims 3-4, and 10) (see e.g. pg. 963, right col., lines 8-21; fig. 2). Borchardt et al. discloses that other type of readout can be use such as secretion of reporter enzymes or translocation of fluorescent proteins (see e.g. pg. 967, right col., lines 34-40). Thus the method of Borchardt et al. anticipates the presently claimed method.

29. Claims 2-4, 10, 18, 33, and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Still et al. (US Patent 5,565,324). *It is noted that this rejection is rewritten to address the newly added claim 54.*

The instant invention recites a method of identifying a test compound that affects a biological event of interest. The method comprises the steps of: 1) providing a plurality of test compounds; 2) providing cells containing an inducible reporter gene, wherein expression of the reporter gene results in the production of a reporter gene product; 3) contacting the cells with the plurality of test compounds; and 4) identifying test compounds which promote or inhibit a biological event based on production of the reporter gene product. The reporter gene product is a) secreted by the cell; b) detectable; and c) its presence indicates occurrence or non-occurrence of a selected biological event.

Still et al. teach methods and composition for encoding combinatorial chemistry (see e.g. Abstract; col. 3, lines 6-45). The methods includes the combinatorial synthesis that employs definable beads upon, which reactions are performed and to which the identifiers are bound, the method of screening the beads carrying the final product compounds for a characteristic of interest, and the method of analyzing the identifier tags attached to the solid supports for the reaction history of the final product compounds (see e.g. col. 3, lines 39-45; col. 5, lines 34-64; col. 29, line 65 to col. 30, line 51; col. 32, lines 14-22). The screening method comprises the steps of: 1) providing a plurality beads carrying the final product compounds (refers to instant claims 10, and 54; and instant claimed step 1) (see e.g. col. 30, lines 1-6); 2) providing cells wherein binding a surface membrane protein (refers to instant claimed reporter gene) produces an observable product (refers to instant claimed reporter gene product) that is expressed (refers to instant claim 18 and instant claimed step 2) (see e.g. col. 30, lines 32-42); 3) the final product compounds is detach from the bead in order to react with the cells (refers to instant claimed step 3) (see e.g. col. 30, lines 13-15); 4) identifying the final product compounds that cause the expression of the observable product (refers to instant claimed step 4) (see e.g. col. 30, lines 42-

44; col. 32, lines 14-22). The final product compounds are attached to the beads via a cleavable linker that can be cleave by irradiation with light (refers to instant claims 3-4) (see e.g. col. 13, lines 44-64). Additionally, the Still et al. also disclosed other type of detachment method such as using chemical reagent, and that the type of detachment method would depend on the type of linker use to attach the product to the bead (see e.g. col. 11, lines 29-64; col. 13, lines 44-64). Furthermore, the identifier tag attached to the solid supports is analyzed for the reaction history of the final product compounds (refers to instant claim 33) (see e.g. col. 6, lines 18-55; col. 26, lines 57-62; col. 32, lines 14-22). Thus the method of Still et al. anticipates the presently claimed method.

30. Claim 55 is rejected under 35 U.S.C. 102(b) as being anticipated by Still et al. (US Patent 5,565,324).

The instant invention recites a method of identifying a test compound that affects a biological event of interest. The method comprises the steps of: 1) providing a plurality of test compounds associated with a plurality of solid supports; 2) providing cells containing an inducible reporter gene, wherein expression of the reporter gene results in the production of a reporter gene product; 3) releasing the tests compounds from the solid supports; 4) contacting the cells with the plurality of released test compounds; and 5) identifying test compounds which promote or inhibit a biological event based on production of the reporter gene product by the detecting agent. The reporter gene product is a) secreted by the cell; b) detected by the detecting agent; and c) its presence indicates occurrence or non-occurrence of a selected biological event.

Still et al. teach methods and composition for encoding combinatorial chemistry (see e.g. Abstract; col. 3, lines 6-45). The methods includes the combinatorial synthesis that employs definable beads upon, which reactions are performed and to which the identifiers are bound, the method of screening the beads carrying the final product compounds for a characteristic of interest, and the method of analyzing the identifier tags attached to the solid supports for the

reaction history of the final product compounds (see e.g. col. 3, lines 39-45; col. 5, lines 34-64; col. 29, line 65 to col. 30, line 51; col. 32, lines 14-22). The screening method comprises the steps of: 1) providing a plurality beads carrying the final product compounds (refers to instant claimed step 1) (see e.g. col. 30, lines 1-6); 2) providing cells wherein binding a surface membrane protein (refers to instant claimed reporter gene) produces an observable product (refers to instant claimed reporter gene product) that is expressed (refers to instant claimed step 2) (see e.g. col. 30, lines 32-42); 3) the final product compounds is detach from the bead in order to react with the cells (refers to instant claimed steps 3 and 4) (see e.g. col. 30, lines 13-15); 4) identifying the final product compounds that cause the expression of the observable product (refers to instant claimed step 5) (see e.g. col. 30, lines 42-44; col. 32, lines 14-22). The final product compounds are attached to the beads via a cleavable linker that can be cleave by irradiation with light (see e.g. col. 13, lines 44-64). Additionally, the Still et al. also disclosed other type of detachment method such as using chemical reagent, and that the type of detachment method would depend on the type of linker use to attach the product to the bead (see e.g. col. 11, lines 29-64; col. 13, lines 44-64). Furthermore, the identifier tag attached to the solid supports is analyzed for the reaction history of the final product compounds (see e.g. col. 6, lines 18-55; col. 26, lines 57-62; col. 32, lines 14-22). Thus the method of Still et al. anticipates the presently claimed method.

Claim Rejections - 35 USC § 103

31. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

32. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

33. Claims 2-4, 10, 18, 26, 33, 53, 54, and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Still et al. (US Patent 5,565,324) and Ashby et al. (US Patent 5,569,588). *It is noted that this rejection is rewritten to address the newly added claims 53, 54, and 68.*

The instant invention recites a method of identifying a test compound that affects a biological event of interest. The method comprises the steps of: 1) providing a plurality of test compounds; 2) providing cells containing an inducible reporter gene, wherein expression of the reporter gene results in the production of a reporter gene product; 3) contacting the cells with the plurality of test compounds; and 4) identifying test compounds which promote or inhibit a biological event based on production of the reporter gene product. The reporter gene product is a) secreted by the cell; b) detectable; and c) its presence indicates occurrence or non-occurrence of a selected biological event.

Still et al. teach methods and composition for encoding combinatorial chemistry (see e.g. Abstract; col. 3, lines 6-45). The methods includes the combinatorial synthesis that employs definable beads upon, which reactions are performed and to which the identifiers are bound, the method of screening the beads carrying the final product compounds for a characteristic of

interest such as physiological or biological activity, and the method of analyzing the identifier tags attached to the solid supports for the reaction history of the final product compounds (see e.g. col. 3, lines 39-45; col. 5, lines 34-64; col. 29, line 65 to col. 30, line 51; col. 32, lines 14-22). The screening method comprises the steps of: 1) providing a plurality beads carrying the final product compounds (refers to instant claims 10, and 54; and instant claimed step 1) (see e.g. col. 30, lines 1-6); 2) providing cells wherein binding a surface membrane protein (refers to instant claimed reporter gene) produces an observable product (refers to instant claimed reporter gene product) that is expressed (refers to instant claim 18 and instant claimed step 2) (see e.g. col. 30, lines 32-42); 3) the final product compounds is detach from the bead in order to react with the cells (refers to instant claimed step 3) (see e.g. col. 30, lines 13-15); 4) identifying the final product compounds that cause the expression of the observable product (refers to instant claimed step 4) (see e.g. col. 30, lines 42-44; col. 32, lines 14-22). The final product compounds are attached to the beads via a cleavable linker that can be cleave by irradiation with light (refers to instant claims 3-4) (see e.g. col. 13, lines 44-64). Additionally, the Still et al. also disclosed other type of detachment method such as using chemical reagent, and that the type of detachment method would depend on the type of linker use to attach the product to the bead (see e.g. col. 11, lines 29-64; col. 13, lines 44-64). Furthermore, the identifier tag attached to the solid supports is analyzed for the reaction history of the final product compounds (refers to instant claim 33) (see e.g. col. 6, lines 18-55; col. 26, lines 57-62; col. 32, lines 14-22).

The method of Still et al. differs from the presently claimed invention by failing to include using yeast cell in the method of screening compounds for a characteristic of interest such as physiological or biological activity.

Ashby et al. teach the methods and compositions for modeling the transcriptional responsiveness of an organism to a candidate drug (see e.g. Abstract; col. 1, lines 40-60). The methods comprise the step of: (a) detecting reporter gene product Signals from each of a plurality of different, separately isolated cells of a target organism, wherein each of said cells contains a recombinant construct comprising a reporter gene operatively linked to a different endogenous transcriptional regulatory element (e.g. promoter) of said target organism such that said transcriptional regulatory element regulates the expression of said reporter gene, wherein said plurality of cells comprises an ensemble of the transcriptional regulatory elements of said organism sufficient to model the transcriptional responsiveness of said organism to a drug; (b) contacting each said cell with a candidate drug; (c) detecting reporter gene product signals from each of said cells; (d) comparing said reporter gene product signals from each of said cells before and after contacting each of said cells with said candidate drug to obtain a drug response profile; wherein said drug response profile provides an estimate of the physiological specificity or biological interactions of said candidate drug (see e.g. Abstract; col. 1, lines 40-60; col. 6, line 51 to col. 8, line 27). The cells include yeast cells (see e.g. col. 2, lines 19-45).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include yeast cell in a cell-based assay for screening compounds for a characteristic of interest such as physiological or biological activity as taught by Ashby et al. in the method of Still et al. One of ordinary skill in the art would have been motivated to include yeast cell in a cell-based assay for screening compounds for a characteristic of interest such as physiological or biological activity in the method of Still et al. for the advantage of model system to obtain preliminary information on compound specificity in higher eukaryotes, such as human

(Ashby: col. 2, lines 19-26). Additionally, both Still et al. and Ashby et al. disclose gene product signal expressed by the cells (Still: col. 30, lines 35-36; Ashby: col. 1, lines 42-43). Furthermore, one of ordinary skill in the art would have reasonably expectation of success in the combination of Still et al. and Ashby et al. because Ashby et al. disclose by example the method of determining the compound characteristic of interest such as physiological or biological activity using yeast cells (Ashby: col. 10, line 34 to col. 11, line 60).

34. Claims 2-7, 9-10, 18-20, 30-31, 33, 53, 54, 57, and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Still et al. (US Patent 5,565,324) and Misko et al. (*Analytical Biochemistry*, **1993**, 214(1), pgs. 11-16). *It is noted that this rejection is rewritten to address the newly added claims 53, 54, 57, and 68.*

The instant invention recites a method of identifying a test compound that affects a biological event of interest. The method comprises the steps of: 1) providing a plurality of test compounds; 2) providing cells containing an inducible reporter gene, wherein expression of the reporter gene results in the production of a reporter gene product; 3) contacting the cells with the plurality of test compounds; and 4) identifying test compounds which promote or inhibit a biological event based on production of the reporter gene product. The reporter gene product is a) secreted by the cell; b) detectable; and c) its presence indicates occurrence or non-occurrence of a selected biological event.

Still et al. teach methods and composition for encoding combinatorial chemistry (see e.g. Abstract; col. 3, lines 6-45). The methods includes the combinatorial synthesis that employs definable beads upon, which reactions are performed and to which the identifiers are bound, the method of screening the beads carrying the final product compounds for a characteristic of interest such as physiological or biological activity, and the method of analyzing the identifier tags attached to the solid supports for the reaction history of the final product compounds (see e.g. col. 3, lines 39-45; col. 5, lines 34-64; col. 29, line 65 to col. 30, line 51; col. 32, lines 14-

22). The screening method comprises the steps of: 1) providing a plurality beads carrying the final product compounds (refers to instant claims 10, and 54; and instant claimed step 1) (see e.g. col. 30, lines 1-6); 2) providing cells wherein binding a surface membrane protein (refers to instant claimed reporter gene) produces an observable product (refers to instant claimed reporter gene product) that is expressed (refers to instant claim 18 and instant claimed step 2) (see e.g. col. 30, lines 32-42); 3) the final product compounds is detach from the bead in order to react with the cells (refers to instant claimed step 3) (see e.g. col. 30, lines 13-15); 4) identifying the final product compounds that cause the expression of the observable product (refers to instant claimed step 4) (see e.g. col. 30, lines 42-44; col. 32, lines 14-22). The final product compounds are attached to the beads via a cleavable linker that can be cleave by irradiation with light (refers to instant claims 3-4) (see e.g. col. 13, lines 44-64). Additionally, the Still et al. also disclosed other type of detachment method such as using chemical reagent, and that the type of detachment method would depend on the type of linker use to attach the product to the bead (see e.g. col. 11, lines 29-64; col. 13, lines 44-64). Furthermore, the identifier tag attached to the solid supports is analyzed for the reaction history of the final product compounds (refers to instant claim 33) (see e.g. col. 6, lines 18-55; col. 26, lines 57-62; col. 32, lines 14-22).

The method of Still et al. differs from the presently claimed invention by failing to include using a nitric oxide molecular sensor for detecting NO synthase activity in a cell based assay that screens compounds for a characteristic of interest such as physiological or biological activity and that the nitric oxide molecular sensor is 2,3-diaminonapthalene (DAN).

Misko et al. disclose a cell based assay for monitoring NA synthase activity using 2,3-diaminonapthalene (DAN) (see e.g. Abstract; pg. 12, left col., line 6-28; pg. 12, right col., line

32-39; pg. 13, left col., line 25 to right col., line 10; pg. 15, right col., line 12 to pg. 16, left col., line 17). This method provides a simple yet sensitive fluorometric determination of NO synthase activity in a 96-well plate format (pg. 11, right col., lines 27-35).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include the use of a nitric oxide molecular sensor for detecting NO synthase activity in a cell based assay that screens compounds for a characteristic of interest such as physiological or biological activity and the nitric oxide molecular sensor is 2,3-diaminonapthalene (DAN) as taught by Misko et al. in the method of Still et al. One of ordinary skill in the art would have been motivated to include the use of a nitric oxide molecular sensor for detecting NO synthase activity in a cell based assay that screens compounds for a characteristic of interest such as physiological or biological activity and the nitric oxide molecular sensor is 2,3-diaminonapthalene (DAN) in the method of Still et al. for the advantage of providing a simple yet sensitive fluorometric determination of NO synthase activity in a 96-well plate format (Misko: pg. 11, right col., lines 27-35). Furthermore, one of ordinary skill in the art would have reasonably expectation of success in the combination of Still et al. and Misko et al. because Misko et al. shown the success of using 2,3-diaminonapthalene (DAN) for detecting NO synthase activity in a cell based assay (Misko: pg. 13, left col., line 25 to pg. 14, right col., line 50).

35. Claims 48, and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Still et al. (US Patent 5,565,324) and Misko et al. (*Analytical Biochemistry*, **1993**, 214(1), pgs. 11-16).

The instant invention recites a method of identifying a test compound that affects a biological event of interest. The method comprises the steps of: 1) providing a plurality of test

compounds; 2) providing cells containing an inducible nitric oxide synthase gene, wherein expression of the reporter gene results in the production of nitric oxide; 3) contacting the cells with the plurality of test compounds; and 4) identifying test compounds which promote or inhibit a biological event based on production of nitric oxide. The presence of the nitric oxide indicates occurrence or non-occurrence of a selected biological event.

Still et al. teach methods and composition for encoding combinatorial chemistry (see e.g. Abstract; col. 3, lines 6-45). The methods includes the combinatorial synthesis that employs definable beads upon, which reactions are performed and to which the identifiers are bound, the method of screening the beads carrying the final product compounds for a characteristic of interest such as physiological or biological activity, and the method of analyzing the identifier tags attached to the solid supports for the reaction history of the final product compounds (see e.g. col. 3, lines 39-45; col. 5, lines 34-64; col. 29, line 65 to col. 30, line 51; col. 32, lines 14-22). The screening method comprises the steps of: 1) providing a plurality beads carrying the final product compounds (refers to instant claimed step 1) (see e.g. col. 30, lines 1-6); 2) providing cells wherein binding a surface membrane protein (refers to instant claimed reporter gene) produces an observable product (refers to instant claimed reporter gene product) that is expressed (refers to instant claimed step 2) (see e.g. col. 30, lines 32-42); 3) the final product compounds is detach from the bead in order to react with the cells (refers to instant claimed step 3) (see e.g. col. 30, lines 13-15); 4) identifying the final product compounds that cause the expression of the observable product (refers to instant claimed step 4) (see e.g. col. 30, lines 42-44; col. 32, lines 14-22). The final product compounds are attached to the beads via a cleavable linker that can be cleave by irradiation with light (see e.g. col. 13, lines 44-64). Additionally, the Still et al. also disclosed other type of detachment method such as using chemical reagent, and that the type of detachment method would depend on the type of linker use to attach the product

to the bead (see e.g. col. 11, lines 29-64; col. 13, lines 44-64). Furthermore, the identifier tag attached to the solid supports is analyzed for the reaction history of the final product compounds (see e.g. col. 6, lines 18-55; col. 26, lines 57-62; col. 32, lines 14-22).

The method of Still et al. differs from the presently claimed invention by failing to include the detection of nitric oxide due to NO synthase activity in a cell based assay that screens compounds for a characteristic of interest such as physiological or biological activity.

Misko et al. disclose a cell based assay for monitoring NA synthase activity using 2,3-diaminonapthalene (DAN) (see e.g. Abstract; pg. 12, left col., line 6-28; pg. 12, right col., line 32-39; pg. 13, left col., line 25 to right col., line 10; pg. 15, right col., line 12 to pg. 16, left col., line 17). This method provides a simple yet sensitive fluorometric determination of NO synthase activity in a 96-well plate format (pg. 11, right col., lines 27-35).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include the detection of nitric oxide due to NO synthase activity in a cell based assay that screens compounds for a characteristic of interest such as physiological or biological activity as taught by Misko et al. in the method of Still et al. One of ordinary skill in the art would have been motivated to include the detection of nitric oxide due to NO synthase activity in a cell based assay that screens compounds for a characteristic of interest such as physiological or biological activity in the method of Still et al. for the advantage of providing a simple yet sensitive fluorometric determination of NO synthase activity in a 96-well plate format (Misko: pg. 11, right col., lines 27-35). Furthermore, one of ordinary skill in the art would have reasonably expectation of success in the combination of Still et al. and Misko et al. because Misko et al. shown the success of using 2,3-diaminonapthalene (DAN) for detecting NO

synthase activity in a cell based assay (Misko: pg. 13, left col., line 25 to pg. 14, right col., line 50).

Response to Arguments

36. Applicant's argument directed to the rejection under 35 U.S.C. 112, first paragraph (written description), for claims 2-7, 9-10, 18-20, 26, and 30-33 have been fully considered but they are not persuasive for the following reasons.

Applicant contends that the instant application meets the written description requirement regarding the presently claimed method of identifying a test compound that affects a biological event of interest using ***any*** type of inducible reporter gene that produced a product, which is secreted by the cell and is detectable because 1) the presently claimed method is a general method that could be practiced using a variety of reporter genes and reporter gene product, and 2) those reporter genes listed in the specification and the one example using nitric oxide synthase would satisfy the written description requirement. Thus the instant application meets the written description requirement regarding the presently claimed method of identifying a test compound that affects a biological event of interest using ***any*** type of inducible reporter gene that produced a product.

Applicant's arguments are not convincing since the instant application does not meet the written description requirement regarding the presently claimed method of identifying a test compound that affects a biological event of interest using ***any*** type of inducible reporter gene that produced a product. As claimed in the instant method, the cells use requires an inducible reporter gene and the expression of the reporter gene results in the production of a reporter gene

product. Although the instant method is "a general method", applicant must have possession of the genus of inducible reporter gene for the practice of the instant claimed method. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. A "representative number of species" means that the species, which are adequately described, are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. That is there is a sufficient variation in the 'type' inducible reporter gene use in the instant claimed invention, e.g. β-lactamase, luciferase, secreted alkaline phosphatase or green fluorescent protein. >The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004). See MPEP § 2163[II(A)2(a)(ii)]. Thus applicant listing in the specification of those reporter genes that can be use in the instant claimed method and the one example using nitric oxide synthase would not satisfy the written description requirement for a claimed genus of the inducible reporter gene because the nitric oxide synthase gene would not produce the 'same' product and is not structurally the 'same' as the β-lactamase

gene. Additionally, the instant application does not disclose any structure, i.e. sequence, of the inducible reporter gene used in the instant claimed method. Therefore, the instant application does not meet the written description requirement regarding the presently claimed method of identifying a test compound that affects a biological event of interest using ***any*** type of inducible reporter gene that produced a product, and the rejection is maintained.

37. Applicant's argument directed to the rejection under 35 U.S.C. 112, first paragraph (written description), for claims 2-3, and 5 have been fully considered but they are not persuasive for the following reasons.

Applicant alleges that the instant application meets the written description requirement regarding the presently claimed method of identifying a test compound that affects a biological event of interest wherein ***any*** type of molecular sensor is use to detect the reporter gene product because "*There are many different molecular sensors known, and one of skill in the art would understand that any of these molecular sensors could be used in the claimed invention*" and the nitric oxide sensor exemplified by the specification disclosure would satisfy the written description requirement. Thus the instant application meets the written description requirement regarding the presently claimed method of identifying a test compound that affects a biological event of interest wherein ***any*** type of molecular sensor is use to detect the reporter gene product.

Applicant's arguments are not convincing since the instant application does not meet the written description requirement regarding the presently claimed method of identifying a test compound that affects a biological event of interest wherein ***any*** type of molecular sensor is use to detect the reporter gene product. As claimed in the instant method, a molecular sensor detects

the reporter gene product expressed by reporter gene of the cell. Although the instant method is "a general method", applicant must have possession of the genus of molecular sensor for the practice of the instant claimed method. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. A "representative number of species" means that the species, which are adequately described, are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. That is there is a sufficient variation in the 'type' molecular sensor use in the instant claimed invention. >The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004). See MPEP § 2163[II(A)2(a)(ii)]. Thus applicant one example using nitric oxide molecular sensor would not satisfy the written description requirement for a claimed genus of the molecular sensor because the nitric oxide molecular sensor is not structurally the 'same' as the molecular sensor such as green fluorescent protein. Therefore, the instant application does not meet the written description requirement regarding the presently claimed method of identifying a

test compound that affects a biological event of interest wherein ***any*** type of molecular sensor is use to detect the reporter gene product, and the rejection is maintained.

38. Applicant's argument directed to the rejection under 35 USC 102(b) as being anticipated by Foulkes et al. (US Patent 5,580,722) for claims 2, 10, 18-20, 26, 30-31, and 54 was considered but they are not persuasive for the following reasons. *It is noted that this rejection is rewritten to address the newly added claim 54.*

Applicant argues that the method of Foulkes et al. does not anticipate the presently claimed method because "*Foulkes et al. does not describe the detection of a reporter gene product that is secreted by the cell*". Thus the method of Foulkes et al. does not anticipate the presently claimed method.

Applicant's arguments are not convincing since the method of Foulkes et al. does anticipate the presently claimed method. Foulkes et al. do disclose a method of detecting the secreted gene product (see col. 12, lines 7-11). Thus, the method of Foulkes et al. does anticipate the presently claimed method, and the rejection is maintained.

39. Applicant's argument directed to the rejection under 35 USC 102(b) as being anticipated by Borchardt et al. (*Chemistry & Biology*, **1997**, 4(12), pgs. 961-968) for claims 2-4, 10, 18, 26, and 54 was considered but they are not persuasive for the following reasons. *It is noted that this rejection is rewritten to address the newly added claim 54.*

Applicant contends that the method of Borchardt et al. does not anticipate the presently claimed method because "*In order for a disclosure to anticipate the claimed invention, it must be*

an enabling disclosure. Borchardt et al. do not provide an enabling disclosure". Thus the method of Borchardt et al. does not anticipate the presently claimed method.

Applicant's arguments are not convincing since the method of Borchardt et al. does anticipate the presently claimed method. In response to applicant argument regarding the enablement of Borchardt et al., the reference of Borchardt et al. is presumed to be enabled and the burden is on applicant to provide facts rebutting the presumption of enablement. (See MPEP § 2121) Applicant has not provided any factual evidence rebutting the presumption of enablement regarding the reference of Borchardt et al. Moreover, applicant's arguments do not rise to the level of factual evidence. See MPEP § 716.01(c): The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Therefore, the method of Borchardt et al. does anticipate the presently claimed method, and the rejection is maintained.

40. Applicant's argument directed to the rejection under 35 USC 102(b) as being anticipated by Still et al. (US Patent 5,565,324) for claims 2-4, 10, 18, 33, and 54 was considered but they are not persuasive for the following reasons. *It is noted that this rejection is rewritten to address the newly added claim 54.*

Applicant alleges that the method of Still et al. does not anticipate the presently claimed method because Still et al. do not disclose that the reporter gene product is secreted from the cell. Thus the method of Still et al. does not anticipate the presently claimed method.

Applicant's arguments are not convincing since the method of Still et al. does anticipate the presently claimed method. Still et al. do disclose that the reporter gene product is secreted

from the cell (see col. 30, lines 33-42). Therefore, the method of Still et al. does anticipate the presently claimed method, and the rejection is maintained

41. Applicant's arguments directed to the rejection under 35 USC 103(a) as being unpatentable over Still et al. (US Patent 5,565,324) and Ashby et al. (US Patent 5,569,588) for claims 2-4, 10, 18, 26, 33, 53, 54, and 68 were considered but they are not persuasive for the following reasons. *It is noted that this rejection is rewritten to address the newly added claims 53, 54, and 68.*

Applicant alleges that the method combination of Still et al. and Ashby et al. is not obvious over the presently claimed method because neither Still et al. nor Ashby et al. disclose that the reporter gene product is secreted from the cell. Thus the method combination of Still et al. and Ashby et al. is not obvious over the presently claimed method.

Applicant's arguments are not convincing since the method combination of Still et al. and Ashby et al. is obvious over the presently claimed method. Still et al. do disclose that the reporter gene product is secreted from the cell (see col. 30, lines 33-42). Therefore, the method combination of Still et al. and Ashby et al. is obvious over the presently claimed method, and the rejection is maintained.

42. Applicant's arguments directed to the rejection under 35 USC 103(a) as being unpatentable over Still et al. (US Patent 5,565,324) and Misko et al. (*Analytical Biochemistry*, **1993**, 214(1), pgs. 11-16) for claims 2-7, 9-10, 18-20, 30-31, 33, 53, 54, 57, and 68 were

considered but they are not persuasive for the following reasons. *It is noted that this rejection is rewritten to address the newly added claims 53, 54, 57, and 68.*

Applicant argues that the method combination of Still et al. and Misko et al. is not obvious over the presently claimed method because 1) Still et al. do not disclose that the reporter gene product is secreted from the cell, and 2) there is no motivation to combine the teaching of Still et al. and Misko et al. Thus the method combination of Still et al. and Misko et al. is not obvious over the presently claimed method.

Applicant's arguments are not convincing since the method combination of Still et al. and Misko et al. is obvious over the presently claimed method. First, Still et al. do disclose that the reporter gene product is secreted from the cell (see col. 30, lines 33-42). Second, in response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to combine the teaching of Still et al. and Misko et al. is found in the reference of Misko et al., i.e. for the advantage of providing a simple yet sensitive fluorometric determination of NO synthase activity in a 96-well plate format (Misko: pg. 11, right col., lines 27-35). Thus, there is a motivation to combine the teaching of Still et al. and Misko et al. Therefore, the method combination of Still et al. and Misko et al. is obvious over the presently claimed method, and the rejection is maintained.

Conclusion

43. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to My-Chau T. Tran whose telephone number is 571-272-0810. The examiner can normally be reached on Monday: 8:00-2:30; Tuesday-Thursday: 7:30-5:00; Friday: 8:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

mct
March 20, 2005

PADMASHRI PONNALURI
PRIMARY EXAMINER